PATENT SPECIFICATION

NO DRAWINGS

929,403

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Date of Application and filing Complete Specification Nov. 9, 1959.

No. 37942/59.

Application made in United States of America (No. 781920) on Dec. 22, 1958.

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Index at acceptance:—Class 81(1), A, B(3:4:6).

International Classification:—A61j, k.

COMPLETE SPECIFICATION

Encapsulated Emulsions and Processes for their P[illegible]

SPECIFICATION NO. 929,403

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of THE NATIONAL CASH REGISTER COMPANY, of Dayton, Ohio, United States of America, a Corporation organised and existing under the laws of the State of Maryland, United States of America

lowing statement:—

This invention relates to a process of encapsulation by liquid-liquid phase separation and to products resulting therefrom, and more particularly to a process for coacervation for encapsulating particles consisting of a hydrophilic liquid-in oil emulsion and to the products thereof.

As employed herein, the term lipophilic is applied to those surfaces having stronger attractive forces for low dielectric constant and non-polar media than for high dielectric constant and polar media. The term "hydrophilic" refers to those surfaces having relaphilic" refers to those surfaces having stronger attractive forces for high dielectric constant and polar media than for low dielectric constant and non-polar media.

According to the novel process of this invention, the novel products hereof are prepared by first forming a primary hydrophilic liquid-in-oil emulsion (the oil being a lipophilic liquid) containing an anti-inversion agent in the oil phase to prevent the inversion of the said emulsion. The said primary emulsion is then dispersed in an aqueous dispersion of at least two coacervating colloids, at least one of which is gelable and at least one of which is an isoelectric colloid, at a temperature above the gel point of the said gelable colloid. Dilution of the resulting double or secondary emulsion with water or adjustment of the pH causes a coacervate to deposit about the particles composed of the primary emulsion.

Liquid-liquid phase separation refers to the [illegible] vate is a polymer-rich sol which has separated from an original single-phase polymeric dispersion (either a solution or a sol), leaving behind a polymer-poor sol or equilibrium liquid. The coacervate appears initially as a fine dispersion of microscopic droplets of polymer in the equilibrium liquid. When formed in a pure colloidal system, these droplets are essentially homogeneously dispersed. However, if foreign materials are present in the original dispersion, the coacervate tends to form around these materials. Technically, the term coacervation therefore relates to the process by which the liquid colloidal concentrate or coacervate is formed as a phase entity of the initial sol or solution. In its practical aspect, and as employed herein, coacervation relates to the process by which foreign materials present in the sol when the coacervate is formed are enveloped or encapsulated by the coacervate. Where the coacervate consists of a single colloid, the process is termed simple coacervation; where more than one colloid is present in the coacervate, as herein, the process is called complex coacervation.

Coacervation has long been known as a phenomenon primarily of academic interest, and only in recent years has it been developed in certain limited aspects for commercial utilization. However, even with this renewed interest in the subject, the technique has been successfully described only for the coating of oil droplets per se and of oil droplets containing dissolved or dispersed materials. British Patent Specification 751,600 discloses methods for encapsulating oil droplets by co-

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COMPLETE SPECIFICATION

Encapsulated Emulsions and Processes for their Preparation

We, THE UPJOHN COMPANY, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 301, Henrietta Street, Kalamazoo, State of Michigan, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to a process of encapsulation by liquid-liquid phase separation and to products resulting therefrom, and more particularly to a process for coacervation for encapsulating particles consisting of a hydrophilic liquid-in oil emulsion and to the products thereof.

As employed herein, the term lipophilic is applied to those surfaces having stronger attractive forces for low dielectric constant and non-polar media than for high dielectric constant and polar media. The term "hydrophilic" refers to those surfaces having relaphilic" refers to those surfaces having stronger attractive forces for high dielectric constant and polar media than for low dielectric constant and non-polar media.

According to the novel process of this invention, the novel products hereof are prepared by first forming a primary hydrophilic liquid-in-oil emulsion (the oil being a lipophilic liquid) containing an anti-inversion agent in the oil phase to prevent the inversion of the said emulsion. The said primary emulsion is then dispersed in an aqueous dispersion of at least two coacervating colloids, at least one of which is gelable and at least one of which is an isoelectric colloid, at a temperature above the gel point of the said gelable colloid. Dilution of the resulting double or secondary emulsion with water or adjustment of the pH causes a coacervate to deposit about the particles composed of the primary emulsion.

Liquid-liquid phase separation refers to the separation of a solution or a sol of a polymer or colloid or combination of polymers or colloids into two distinct liquid phases, one designated as the polymer-rich phase and the other the polymer-poor phase. Where the polymer-rich and polymer-poor phases are colloidal sols rather than true solutions, the phenomenon of phase separation is herein designated as coacervation. Thus, a coacervate is a polymer-rich sol which has separated from an original single-phase polymeric dispersion (either a solution or a sol), leaving behind a polymer-poor sol or equilibrium liquid. The coacervate appears initially as a fine dispersion of microscopic droplets of polymer in the equilibrium liquid. When formed in a pure colloidal system, these droplets are essentially homogeneously dispersed. However, if foreign materials are present in the original dispersion, the coacervate tends to form around these materials. Technically, the term coacervation therefore relates to the process by which the liquid colloidal concentrate or coacervate is formed as a phase entity of the initial sol or solution. In its practical aspect, and as employed herein, coacervation relates to the process by which foreign materials present in the sol when the coacervate is formed are enveloped or encapsulated by the coacervate. Where the coacervate consists of a single colloid, the process is termed simple coacervation; where more than one colloid is present in the coacervate, as herein, the process is called complex coacervation.

Coacervation has long been known as a phenomenon primarily of academic interest, and only in recent years has it been developed in certain limited aspects for commercial utilization. However, even with this renewed interest in the subject, the technique has been successfully described only for the coating of oil droplets per se and of oil droplets containing dissolved or dispersed materials. British Patent Specification 751,600 discloses methods for encapsulating oil droplets by co-

acervate coatings of the complex and simple types, respectively. Although the said patent describes the formation of coacervates from an oil-in-water emulsion, only the oil phase is actually encapsulated by the coacervate. Prior to the present invention, the encapsulation of an intact emulsion had not been reported by the coacervation technique, and the important advantages of a coacervate-coated emulsion in which the phases thereof contain dissolved or suspended ingredients have not been heretofore obtainable.

It has now been unexpectedly found, however, that particles consisting of a primary hydrophilic liquid-in-oil emulsion constituting the dispersed phase of a secondary or double emulsion can be encapsulated by complex coacervation if the oil phase of the primary emulsion contains a substance, herein designated an anti-inversion agent, capable of preventing the inversion of the hydrophilic liquid-in-oil emulsion to an oil-in-hydrophilic liquid emulsion in the course of coacervation.

It has likewise been found that a further improvement in the efficiency of the coacervation process and in the properties of the resulting encapsulated product can be realized by the addition of a thickening agent to the hydrophilic liquid phase of the primary emulsion to fix any dissolved or suspended active ingredients, as hereinafter specified, therein during coacervation, and it is sometimes also found to be advantageous to add a thickening agent to the coacervating medium.

The present process and products resulting therefrom afford a new approach to the provision of impermeable coatings of high strength or coatings which permit a gradual release of contents for water-soluble materials broadly, a problem which has heretofore resisted solution by the known techniques of coacervation. For example, encapsulated emulsion particles can be prepared containing appropriate active ingredients in the emulsion phases for use as sustained release fertilizers, plant growth hormones and pesticides such as fungicides, nematocides, bactericides, viricides and the like for agricultural use. In addition, active ingredients can be incorporated in premixed foods which could not normally be included because of loss in the drying step, the encapsulated ingredients being liberated by the shearing force exerted in a mixing step prior to actual use. Similarly, vitamins, notably combinations of water-soluble and oil-soluble vitamins, can be incorporated into dry cereal preparations for release in the body. Cosmetics can be prepared in which the topical agent is enclosed by impermeable but readily destructible coacervate shells. Pharmaceutical materials can be encapsulated for sustained or delayed release in the body upon contact with a predetermined pH environment or enzyme system, or where stability, odour, taste or incompatibility problems are present. Such materials can be enclosed in coatings suitable for oral, topical or injectable use by regulation of the particle size and coating thickness, permeability and hardness or by selection of coacervating components. Insecticides with selective toxicity for insects but which are relatively non-toxic toward humans can be encapsulated, for example, with coacervate coatings which are highly impermeable except in the presence of enzymes of the insects. Rodenticides which are effective on ingestion by the animals but which have odours that forwarn or repel them can likewise be coated by the method of this invention with virtually complete impermeability with respect to the odour.

Complex coacervation in the process of this invention involves the separation of at least two hydrophilic colloids as coacervating colloids into two phases, one of which contains the coacervating colloids in high concentration and the other of which contains coacervating colloids in relatively low concentration, these phases being known as the colloid-rich and the colloid-poor phases, respectively. It is essential in this invention that, for coacervation to occur, the pH of the coacervating medium is such that there are present therein colloids of opposite charges. The coacervating medium is the mixture of aqueous sols or solutions of the coacervating colloids prior to coacervation.

At least one of the coacervating colloids must be gelable and at least one must be isoelectric, by which we mean a colloid whose molecules contain both acidic and basic functions. Thus, one of the colloids may be gelable while a second colloid is isoelectric. However, there may be present at least one colloid which is both isoelectric and gelable while the other colloid or colloids present in the coacervating medium may be gelable, or isoelectric, or both, or neither but if they are neither isoelectric or gelable then they must be capable of having an electric charge. Whatever combination of colloids is present coacervation will occur only when there are present in the coacervating medium colloids of opposite charge and in order for such colloids to be present the pH of the coacervating medium must lie within the coacervating range for the particular combination of colloids. The coacervating range is dependent on the particular combination of colloids present.

If the pH of the coacervating medium lies within the coacervating range for the particular colloids present in the medium then dilution of the medium will cause coacervation although coacervation may also be brought about by suitably adjusting the pH of the coacervating medium within the coacervating range. If the pH of the coacervating medium lies outside the coacervating

range then it must be adjusted to a value within the range and the coacervating medium may then be diluted to cause coacervation as before.

The term "coacervating colloids" refers to naturally occurring gelable and non-gelable hydrophilic colloids and examples of the coacervating colloids are gelatin, agar-agar, albumen, alginates, casein, pectins, acacia, starch, fibrinogen, starch acetate phthalate, cellulose acetate phthalate and amylose acetate phthalate and collagen. Of these, the following are isoelectric colloids: gelatin, albumen, casein, fibrinogen and collagen; and the following are gelable hydrophilic colloids: gelatin, agar-agar, albumen, casein, pectins and fibrinogen, collagen, starch acetate phthalate, cellulose acetate phthalate and amylose acetate phthalate.

The term "hydrophilic liquid" herein refers to water, aqueous solutions or suspensions, and non-aqueous solutions or suspensions immiscible in the oil phase of the primary emulsion. As used herein the term "active ingredient" refers to material which may be included in either or both phases of the primary emulsion and which does not substantially affect the emulsification or coacervation process.

In addition to emulsions containing soluble or suspendable active ingredients in the hydrophilic liquid phase, the coacervates herein, by practice of the present invention, can be deposited about an emulsion containing dissolved or suspended active ingredient in the oil phase. The active ingredients to be dissolved or suspended in either the hydrophilic liquid or the oil phases are limited in selection only by the solubility, suspending chracteristics or compatibility of the ingredients in both phases.

As employed herein, the term "primary emulsion" is intended to refer to the emulsion initially formed from the hydrophilic liquid, with or without dissolved or suspended active ingredients, and the selected oil, with or without dissolved or suspended active ingredients. The selection of the said oil is not critical and is dependent on the function to be served by the oil, i.e., as a solvent or suspending medium or merely as the external phase of the primary emulsion. Thus, virtually any animal, vegeable, mineral or synthetic oil having the desired physical characteristics can be employed for this purpose. Lanolin, corn oil, soyabean oil, castor oil, cod liver oil, and mineral oil are examples of such oils. The conventional emulsifying agents, such as esters of polyhydric alcohols, sorbitan fatty acid esters and sorbitan polyoxyethylene fatty acid esters are usually employed in preparing the said primary emulsion.

Selection of the particular surface active agent or combination of agents for any particular emulsion can advantageously be made by reference to the HLB (hydrophile-lipophile balance) system, as described in Remington's Practice of Pharmacy, 11th Edition, Mack Publishing Company, 1956, page 191. Thus, by noting the HLB requirement for the particular emulsion system involved, an appropriate agent or combination of agents can be identified which will facilitate the stabilization of the desired emulsion. As with all emulsion formation problems, selection of the most suitable agents must ultimately be based on trial. Accordingly, a sample of the final emulsion should be checked, for example, by diluting and agitating with a relatively large volume of water, to determine that a stable emulsion of the type desired has actually been obtained. Additionally, the selected agents must be compatible with the formation of a coacervate.

The term "anti-inversion agent" as used herein refers to any material capable of preventing the inversion of the primary hydrophilic liquid-in-oil emulsion to an oil-in-hydrophilic liquid emulsion on dispersion of the said primary emulsion in the "coacervating medium" to form the "secondary emulsion". Materials contemplated by the term "anti-inversion agent" include surface active agents, preferably those of the nonionic type, and oil-thickening agents such as the natural and synthetic waxes, solid fats, sterols and other conventional oil-gelling or oil-thickening agents. Examples of the said surface active agents include the sorbitan fatty acid esters and the polyoxyethylene sorbitan fatty acid esters. The said oil-thickening agents include, for example, beeswax, carnaubu wax, paraffin wax, saturated fatty acid esters, sitosterol, cholesterol, stigmasterol, and hydrogenated castor oil. The oil-thickening agents, including the oil-gelling agents, suitable for use as anti-inversion agents are those which are retained in the oil, i.e., agents having a higher heat of immersion in the hydrophilic liquid than in the oil. No generalization can be made regarding the amount of thickening agent required as the anti-inversion agent in any given emulsion system, as the amount will vary with the specific oil included therein; routine testing of the stability of the desired emulsion on dilution with water will indicate the necessary concentration. It is essential in the process of this invention that the oil phase of the primary emulsion contains an anti-inversion agent and, as this, in some cases, is the same as or similar to one of the conventional emulsifying agents, it is not always necessary to use additional emulsifying agent to stabilise the primary emulsion.

The thickening agents used herein are materials which are substantially insoluble in the oil phase of the primary emulsion and are capable of increasing the viscosity of the internal hydrophilic liquid or of the "co-

acervating medium" as hereinafter defined. Suitable agents for this purpose are the known natural and synthetic thickening agents, specifically including those alluded to in "Thickening Agents Used in Pharmacy", by Charles H. Becker, American Professional Pharmacist 20:939 (October) 1954, such as acacia, tragacanth, methyl cellulose, carboxymethylcellulose, and magnesium aluminum silicate, as well as other thickening agents such as the polyglycols, glycerins and syrups. The specific amounts of these materials may vary with the particular agent and system involved and can be readily determined by routine experimentation.

The active ingredients to be dissolved or suspended in the hydrophilic liquid and oil phases are limited in selection only by the solubility, suspending characteristics or compatibility of the active ingredients in both phases.

The term "secondary emulsion" refers to the emulsion formed when the primary emulsion is added to the coacervating medium before coacervation takes place. The said secondary emulsion is in effect a double emulsion comprising the said primary emulsion dispersed in the coacervating medium and exists as an entity of the mixture only until a coacervate is formed about the particles of the secondary emulsion.

In the preferred embodiment of this invention, a primary water-in-oil emulsion is prepared by emulsifying (1) an aqueous solution containing the desired ingredient, together with a small quantity of methyl cellulose as a thickening agent, into (2) approximately an equal volume of a vegetable oil such as corn oil containing a small amount of hydrogenated castor oil as the anti-inversion agent. The preparation of the emulsion is carried out at approximately 55° C. The primary emulsion is added slowly with stirring to an aqueous sol or acacia and gelatin as the coacervating colloids at a temperature of 55° C. to form a double emulsion in the coacervating medium. To the resulting double emulsion is added sufficient water to cause the formation of the coacervate. The thus formed coacervate is then gelled by cooling the equilibrium liquid containing the coacervate to 5° C. over a period of 30 minutes. With the coacervate maintained at this temperature, the pH of the said equilibrium liquid is adjusted to the alkaline side, and formaldehyde solution is introduced to harden the coacervate shell. The hardened coacervate is then washed and dried.

In the preparation of the primary emulsion, the conventional emulsifying agents are normally employed to facilitate the establishment of and contribute to the stability of the primary emulsion, as well as to assure that the correct type of emulsion, i.e., hydrophilic liquid-in-oil, is obtained. Since the size of the final encapsulated emulsion particles depends in part on the size of the emulsion droplets of the primary emulsion, the degree of dispersion of the hyrophilic liquid in the oil should be regulated in accord with the desired particle size of the ultimately obtained coacervate.

The temperature at which the primary emulsion is prepared is of little consequence with respect to the functioning of the present process. However, it is necessary that the temperature at which coacervation is carried out be above the gel point of the coacervating colloids and within or closely approaching the gelling or thickening range of the thickening agent, if any, present in the hydrophilic liquid phase of the primary emulsion in order that the liquid be sufficiently viscous to restrain the escape of active ingredient. Where methyl cellulose is employed as the thickening agent, the temperature of the coacervating medium should be about 50° C. to assure such an increased viscosity in the water phase. After the coacervate shell has enveloped the emulsion particles, the temperature is lowered below the gel point of the coacervating colloid. Where gelatin is employed as a coacervating component, reduction in the temperature to 30° C. or lower, depending on the type of gelatin used, preferably to about 5° C., will produce the desired gelling.

As indicated previously, the secondary emulsion exists during the interval between the first contact of all ingredients in the coacervating medium and the actual formation of the coacervate. The secondary emulsion is a double emulsion consisting of particles of the primary emulsion as the internal phase dispersed in the coacervating medium as the external phase. If the primary emulsion is added to the aqueous solution of the coacervating colloids, the double or secondary emulsion will persist until dilution of the sol with water is carried to the point at which coacervation occurs. The critical concentration of the colloids will vary with the particular colloids involved and can be readily determined by conducting a test run in the absence of emulsions. A developing cloudiness in the coacervation medium in the course of dilution marks the concentration at which coacervation begins, and the presence of an emulsion tends to obscure a change in turbidity.

Alternatively, coacervation can be induced by adjusting the pH of the coacervating medium to the particular pH range operative for the coacervating components involved. For every combination of coacervating colloids there exists a pH range within which coacervation will occur. This range can be determined by the method described above.

The ultimate particle size of the coacervate product is dependent in part, as here-

tofore indicated, on the degree of dispersion or size of the emulsion particles of the primary emulsion. In addition, the particle size is of course a function of the thickness of the coacervate coating. The more complete and rapid the mixing, the smaller the secondary emulsion droplets which are presented as nuclei about which the coacervate will form, and hence the smaller will be the final coacervate units.

The gelling step is significant with respect to the permeability of the coacervate membrane. With many coacervate systems, instantaneous gelling the the warm coacervate, as by adding the warm coacervate to ice water, produces a coacervate membrane having high permeability. A prolonged period of slow cooling also favors a membrane of relatively high permeability. With many coacervate systems the lowest permeability (or highest impermeability) is obtained with intermediate cooling rates. Thus, a relatively impermeable coacervate coating is produced in the case of a gelatin-acacia coacervate on cooling the newly-formed coacervate to about 5° C. in a period of approximately 30 minutes with continuous stirring.

Following gelation of the liquid coacervate, the gelled coacervate optionally can be hardened, plasticized or otherwise treated to adapt it to the intended use. Treating the gelled coacervate, for example, with a 37% aqueous solution of formaldehyde under alkaline conditions produces a hardened coacervate shell which can then be dried. For most applications, contact of the coacervate with the said formaldehyde solution for a period of about 10 minutes is productive of a material having substantially improved hardness qualities over the untreated coacervate.

Variations in the hardness of the coacervate shell can be obtained by varying the quantity of hardening agent and/or the period of contact therewith. Hardening has considerable influence on the permeability of the coacervate, both with respect to the invasion of environmental fluids which would cause disintegration of the coating and to the containment of ingredients which would otherwise impart undesirable color or taste characteristics to the product.

The finally treated coacervate can be separated by a method such as centrifuging, filtering or decanting. This can be followed by drying by known methods, such as spray drying, freeze drying, air drying or direct heating, optionally preceded by a washing step, to obtain a product essentially free of surface moisture. Such a product can then be formulated as a dry material.

A convenient and informative test for the integrity of coacervate coating produced by the method of the present invention involves the incorporation of a soluble dye in the hydrophilic liquid phase of the primary emulsion. The coacervate is formed in the manner described and the resulting material, after gelling and, optionally, after hardening, is dispersed or immersed in the test liquid. The liquid is gently stirred to thoroughly expose all coacervate surfaces. Any dye escaping from the hydrophilic liquid phase through the coacervate shell is readily detectable in the test liquid.

The following examples are illustrative of the process and products of the present invention but are not to be construed as limiting the scope of the invention.

EXAMPLE 1.

A water-in-oil emulsion is prepared by emulsifying at 40° C. a solution of 25 gm. of urea in 25 ml. of water into 40 ml. of peanut oil containing 5 gam. of beeswax. A sol is prepared by dissolving at 40° C. 27 gm. of gum acacia and 20 gm. of gelatin in 350 ml. of water. With continuous stirring, the emulsion is added to the sol to form a double emulsion of the oil droplets containing dispersed urea solution in the sol. To the emulsion-sol mixture is added, dropwise and with continuous stirring, 600 ml. of water previously heated to 40° C., thereby causing the coacervate to form. The temperature of the coacervating medium is lowered to 5° C. to gel the coacervate. Sufficient 10 percent sodium hydroxide solution is added to raise the pH to about 10, and 20 ml, of 37 percent formaldehyde solution is added to the resulting product to harden the coacervate shell. The mixture is allowed to stand for 4 hours at 5° C. The hardened coacervate is then separated from the mixture by centrifugation, washed and dried.

In this example gelatin serves as both the isoelectric and gelable colloid while acacia is neither.

The above composition can be employed as a fertilizer in which the nitrogen is made available over a prolonged period through slow release of the urea.

Other aqueous solutions and aqueous suspensions of water-and oil-insoluble ingredients can likewise be employed as the hydrophilic liquid of the primary emulsion above.

Instead of diluting the emulsion-sol mixture to cause formation of the coacervate, coacervation can be induced by adjusting the pH.

The foregoing process is likewise operable with other anti-inversion agents substituted for the beeswax employed above, e.g., nonionic surface active agents and hydrophobic oil-gelling or oil-thickening agents such as natural and synthetic waxes, hydrogenated castor oil, solid fats and sterols. Likewise, other oils can be selected as the external phase of the primary emulsion. Instead of gelatin and gum acacia as the coacervating colloids, other combinations of hydrophilic

colloids can be used, such combinations being selected from among such colloids as agar-agar, albumen, alginates, casein, pectins, starch and fibrinogen. In selecting the colloid combination, it should be remembered that one colloid must be gelable and one must be an isoelectric colloid.

EXAMPLE 2.

A suspension of 100 gm. of micronized caffeine in 100 ml. of water is prepared at 50° C. A mixture of 50 gm. of sitosterol and 150 ml. of corn oil is likewise prepared at 50° C. The caffeine suspension is emulsified into the oil mixture by passing the materials together through a colloid mill. Two hundred grams of collagen and 200 gm. of sodium alginate are dispersed in 8 litres of water and heated to 50° C. The resulting dispersion is raised to pH 7 with 10% sodium hydroxide solution. With continuous stirring of the collagen-alginate sol, the caffeine aqueous suspension corn oil emulsion is dispersed therein. Stirring is continued for 10 minutes with the temperature maintained at 50° C. Dilute acetic acid is then added dropwise with continuous stirring to lower the pH to 3.2. Stirring is continued for an additional 30 minutes and the resulting coacervate is cooled to 5° C. over a period of 30 minutes, separated by centrifuging and freeze dried at −40° C.

In this example, collagen serves as both a gelable and isoelectric colloid while sodium alginate is isoelectric.

EXAMPLE 3.

A water-in-oil emulsion is prepared by emulsifying at 50° C. 50 ml. of water in which is dissolved 0.5 gm. of D. & C. green dye No. 5 and 0.5 gm. of methyl cellulose into 50 ml. of mineral oil containing 0.5 gm. of sorbitan monooleate. A sol comprising 25 gm. of gum acacia and 25 gm. of gelatin in 300 ml. of water is heated to 50° C. The emulsion is added to the sol with continuous stirring. Seven hundred milliliters of water, previously heated to 50° C. is added dropwise with continuous stirring to the emulsion-sol mixture. The temperature of the mixture is lowered to 5° C. to gel the coacervate. Sufficient 10% sodium hydroxide solution is added to bring the pH up to 9.5, followed by the addition of 25 ml. of 37% formaldehyde solution. The hardened coacervate is then filtered from the mixture, washed and dried.

In this example, methyl cellulose is used as a thickening agent and gelatin as both an isoelectric and gelable colloid while acacia is neither.

EXAMPLE 4.

A water-in-oil emulsion is prepared by emulsifying at 50° C. 75 ml. of water in which is dissolved 0.75 gm. of D. & C. green dye No. 5 and 0.75 gm. of tragacanth into 75 ml. of mineral oil containing 1.0 gm. of hydrogenated castor oil. A sol is prepared at 50° C. from 50 gm. of gelatin, 30 gm. of acacia, 20 gm. of carboxymethylcellulose, and 600 ml. of water. The emulsion is added slowly to the sol with continuous stirring. To the emulsion-sol mixture is added dropwise 1500 ml. of water, previously heated to 50° C., to gel the coacervate. Sufficient 10% sodium hydroxide solution is added to bring the pH to about 9.5, and 50 ml. of formaldehyde solution is introduced to harden the coavervate shell. The hardened coacervate is then separated from the coacervating medium by centrifugation, washed and dried.

In this example, tragacanth and carboxymethylcellulose are thickening agents, gelatin is both an isoelectric and a gelable colloid and acacia is neither.

EXAMPLE 5.

A glycerin-in-oil emulsion is prepared by emulsifying at 50° C. 50 ml. of glycerin into 50 ml. of peanut oil containing 0.5 gm. of hydrogenated castor oil. A sol is prepared from 27 gm. of gum acacia and 20 gm. of gelatin in 350 ml. of water heated to 50° C. The emulsion is added slowly to the sol with continuous stirring. To the emulsion-sol mixture is added dropwise 650 ml. of water previously heated to 50° C. The temperature of the mixture is lowered to 5° C. to gel the coacervate. Sufficient 10% sodium carbonate solution is introduced to raise the pH of the mixture to about 9.5, and 20 ml. of 37% formaldehyde solution is added to harden the coacervate shell. The then hardened coacervate is separated from the mixture by centrifugation, washed and dried.

In this example, gelatin is both an isoelectric colloid and an isoelectric colloid while acacia is neither.

EXAMPLE 6.

Two grams of tragacanth and 0.6 gm. of D. & C. green dye No. 5 are dispersed in 60 ml. of glycerin, and the dispersion is heated to 40° C. Twenty grams of paraffin wax are added to 40 gm. of petrolatum and the resulting mixture heated to 40° C. The glycerin solution is emulsified into the paraffin-petrolatum mixture. A dispersion of 50 gm. of serum albumin is prepared in 250 ml. of water and heated to 40° C. Sufficient 20% acetic acid is added to bring the pH to 3.0. The emulsion is then dispersed into the albumin sol with continuous stirring. Thereafter, 50 gm. of acacia is dispersed in 250 ml. of water and heated to 40° C. The pH of the resulting dispersion is adjusted to 3.0 with 20% acetic acid. The acacia sol is added dropwise to the emulsion mixture with continuous stirring. Immediately thereafter, 700 ml. of water previously heated to 40° C. is added dropwise, the temperature being main-

tained at 40° C. and stirring continued for 30 minutes. The resulting coacervate is cooled to 4° C., filtered, washed and dried.

In this example, tragacanth is a thickening agent, alubumin is both an isoelectric and gelable colloid and acacia is neither.

WHAT WE CLAIM IS:—

1. A process for coating particles of a hydrophilic liquid-in-oil emulsion which comprises forming a primary hydrophilic liquid-in-oil emulsion containing an anti-inversion agent as hereinbefore defined in the oil phase, dispersing the said primary emulsion in an aqueous dispersion of at least two coacervating colloids at least one of which is gelable and at least one of which is an isoelectric colloid at a temperature above the gel point of the gelable coacervating colloid to form a coacervating medium and causing a coacervate to deposit about particles composed of the primary emulsion.

2. A process as claimed in Claim 1 wherein the hydrophilic liquid and/or the oil used in forming the primary hydrophilic liquid-in-oil emulsion contains dissolved or suspended active ingredients as hereinbefore specified.

3. A process as claimed in Claim 1 or 2 wherein the primary hydrophilic liquid-in-oil emulsion is formed by emulsifying the hydrophilic liquid and an animal, vegetable, mineral or synthetic oil in the presence of an emulsifying agent.

4. A process as claimed in any preceding claim in which the anti-inversion agent is a non-ionic surface active agent or an oil-thickening agent.

5. A process as claimed in Claim 4 in which the anti-inversion agent is hydrogenated castor-oil, beeswax, sorbitan monooleate or sitosterol.

6. A process as claimed in any preceding claim in which the coacervating medium contains a thickening agent.

7. A process as claimed in Claim 6 in which the thickening agent is acacia.

8. A process as claimed in any preceding claim in which the hydrophilic liquid is water.

9. A process as claimed in any preceding claim in which the coacervate is caused to deposit by dilution of the coacervating medium with water.

10. A process as claimed in any preceding claim in which the particles coated by the coacervate are cooled to at least the gel point of the gelable coacervating colloid to gel the gelable coacervating colloid.

11. A process as claimed in Claim 10 in which the coacervate is separated by centrifuging, filtering or decanting and then subjected to spray drying, freeze drying, air drying or direct heating to obtain a product having an essentially dry surface.

12. A process for coating particles of a water-in-oil emulsion which comprises preparting a primary water-in-oil emulsion by emulsifying an aqueous solution containing an active ingredient as hereinbefore specified together with methyl cellulose into about an equal volume of a vegetable oil containing hydrogenated castor oil, slowly adding the primary emulsion with stirring to an aqueous sol of acacia and gelatin at a temperature of 55° Centigrade, adding sufficient water to the resulting double emulsion to cause the formation of the coacervate, gelling the thus formed coacervate by cooling the equilibrium liquid containing it to 5° Centigrade over a period of 30 minutes, adjusting the pH of the equilibrium liquid to alkaline and introducing formaldehyde solution to harden the coacervate shell and then washing and drying the hardened coacervate.

13. A process as claimed in Claim 12 wherein the vegetable oil used is corn oil and the emulsification is carried out at about 55° Centigrade in the presence of an emulsifying agent.

14. A capsule comprising a hydrophilic liquid-in-oil emulsion enclosed within a complex coacervate coating, at least one component of which is a gelable colloid and at least one component of which is an isoelectric colloid.

15. A capsule as claimed in Claim 14 in which the hydrophilic liquid is water.

16. A capsule as claimed in Claim 14 and 15 in which the hydrophilic liquid-in-oil emulsion contains a dissolved or suspended active ingredient as hereinbefore specified.

17. A process for the preparation of an encapsulated hydrophilic liquid-in-oil emulsion substantially as herein described with reference to any of the examples.

18. An encapsulated hydrophilic liquid-in-oil emulsion when prepared by a process as claimed in any of Claims 1 to 12 or 17.

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